REMARKS

Claims 26-35 were pending. Claim 26 is amended without prejudice to renewal or refiling of the original scope. Claims 1-25, 31-32 and 34 are canceled. No new matter is added.

The claims are amended to introduce language directed a host cell where an antibiotic resistance gene and an antibiotic sensitivity gene are present at a heterologous recombination site, such that the two genes are eliminated when the functional site specific recombinase is present. This is the situation exemplified in Figure 6, note the genetic structure shown in Figure 6A where the TetR and StrepS genes are flanked by the Lox sites. This Figure is described in detail in Example 4, e.g. see page 32, lines 18-27.

The specific amending language is as follows, "the bacterial host further having, between heterologous recombination sites, an antibiotic resistance gene and an antibiotic sensitivity gene."

As used in the certain embodiments of the invention, in the presence of active site specific recombinase, the antibiotic resistance gene and the antibiotic sensitivity gene of the heterologous recombination site are deleted and bacterial transformants cannot grow in the presence of an antibiotic for said antibiotic resistance gene, providing for selection of bacterial transformants containing a first DNA sequence of interest that is complementary to a second DNA sequence of interest. In the presence of inactive site specific recombinase, the antibiotic resistance gene and the antibiotic sensitivity gene of the heterologous recombination site are maintained and the bacterial transformants grow in the presence of an antibiotic for said antibiotic resistance gene but not in the presence of an antibiotic for said antibiotic sensitivity gene, providing for selection of bacterial transformants containing a first DNA sequence of interest that differs from a second DNA sequence of interest by a mismatch of from 1 to 4 contiguous nucleotides in length.

Support for the amending language may be found in the specification at page 11, lines 11-17; and page 9, lines 27-29.

Claims 34-35 have been rejected under 35 U.S.C. 112, second paragraph. The limitations of Claim 34 have been added to independent Claim 26, and the language has been clarified to state that the detectable marker is a gene encoding a site specific recombinase.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 26-32 have been rejected under 35 U.S.C. 102(b) as anticipated by Parker *et al.* (1992). Without conceding to the correctness of the rejection, applicants have amended independent Claims 26 and 28 to introduce the limitations of previously presented Claim 34. In view of the above amendments, Applicants respectfully submit that the rejection is made moot.

Claims 26-33 have been rejected under 35 U.S.C. 102(b) as anticipated by Carraway *et al.* (1993). Without conceding to the correctness of the rejection, applicants have amended independent Claims 26 and 28 to introduce the limitations of previously presented Claim 34. In view of the above amendments, Applicants respectfully submit that the rejection is made moot.

Claims 26, 27, 31, 32, 34 and 35 have been rejected under 35 U.S.C. 102(b) as anticipated by Sternberg et al. (1986). Applicants respectfully submit that the presently claimed invention is not taught or suggested by the cited art. Without conceding to the correctness of the rejection, applicants have amended independent Claim 26 to recite the inclusion of an MMR strain of competent host bacteria having an antibiotic resistance gene and an antibiotic sensitivity gene between heterologous recombination sites. The cited prior art fails to teach the use of such a host strain.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 34 and 35 have been rejected under 35 U.S.C. 103(a) as unpatentable over Carraway *et al.* (1993) in view of Zambrowicz, U.S. Patent no. 6,080,576. Without conceding to the correctness of the rejection, applicants have amended independent Claim 26 to introduce the limitations of previously presented Claims 34, and have amended independent Claim 26 to recite the inclusion of an MMR strain of competent host bacteria having an antibiotic resistance gene and an antibiotic sensitivity gene between heterologous recombination sites. With respect to the application of the obviousness rejection to presently pending Claim 26, Applicants respectfully submit that the present claims are not taught or suggested by the cited art.

The Office Action states that Carraway *et al.* teach a kit comprising a first DNA vector comprising a first DNA vector encoding a detectable marker, an origin of replication active in a bacterial cell and a sequence of interest, wherein the vector lacks methyl adenine; and a second methylated DNA vector that is substantially complementary but has an inactivating mutation of 5, 192 or 410 nucleotides.

The Office Action further states that Zambrowicz teaches a variety of genes can function as known equivalent markers, including antibiotic resistance genes, enzymes, fluorescent marker genes, and specifically cre and flp genes. It is asserted that site specific recombinase genes are known as equivalent to antibiotic resistance markers. Applicants respectfully submit that such markers are not equivalent.

The presently claimed kit allows the practice of a method where a marker which is a recombinase, *e.g. cre* recombinase, FLP recombinase, pSR1 recombinase, *etc.*, which is indirectly detected. For example, the presence of active *cre* may be detected by recombination between two or more heterologous recombination sites, where a directly detectable marker is present between these recombination sites. The active enzyme will recombine between the sites, thereby deleting the directly detectable marker; while in the presence of inactive enzyme the directly detectable marker is maintained.

These feature – a site specific recombinase and a host cell having an antibiotic resistance and an antibiotic sensitivity marker provide for a coordinate system of three separate elements for selection. By combining these multiple elements, the system is provides a number of advantages. There is an internal method of verification, *i.e.* both growth and lack of growth for either DNA configuration (a mismatch is present or a mismatch is not present). Further, the present methods allow selective growth in either DNA configuration, thereby providing a means of readily isolating DNAs from both configurations.

The presently claimed kit provides for convenient selection of both variant sequences and non-variant sequences by what is, in essence, a molecular switch that is implemented by the presence or absence of a functional Cre gene product and the use of two different selective growth media. That is, it is much more than a mere swapping between equivalent markers.

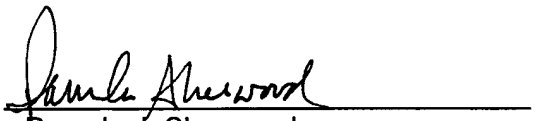
Applicants respectfully submit that the present claims meet the requirements for patentability under 35 U.S.C. 103(a). Withdrawal of the rejection is requested.

CONCLUSION

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number UCSF-127CON2.

Respectfully submitted,
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